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10/019,067	06/28/2002	Mats Paulsson	HLZ-001US	7795

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,067	PAULSSON ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16 and 26-31* is/are pending in the application.

4a) Of the above claim(s) *15,16 and 26-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/19/03, 12/05/05, 03/26/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, Claims 13-16 and 26-31 in the reply filed on October 28, 2005 is acknowledged. Also, Applicants election of the species "dermatitis herpetiformis" and "morbus Duhring" in the reply filed August 7, 2006 is acknowledged. It is also noted that Applicant's have stated that "dermatitis herpetiformis" and "morbus Duhring" are two different names for the same disease. Thus, claims 13 and 14 are elected by Applicant and claims 15, 16 and 26-31 are withdrawn as being directed to a non-elected invention.

Specification

2. The disclosure is objected to because of the following informalities: the specification on page 2, lines 26-27 discloses that the invention and preferred modifications thereof are disclosed in claims 1 and 5. Preferred embodiments thereof are described in the dependent claims. The reference to claims in the specification is improper because the claim numbering is subject to change throughout prosecution and thus can cause discrepancies between the specification and the claims. For example, in the current application claims 1 and 5 and dependent claims have been cancelled. Therefore, what is the disclosure referring to? It is recommended to remove any reference to claims from the specification.

3. The disclosure is also objected to because of the following informalities: because on page 21, line 6 the disclosure "hat" should be --that--.

Appropriate correction is required.

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing gluten sensitive enteropathy by testing a sample for IgA antibodies directed against human tissue transglutaminase and TGe and correlating increased amounts of the IgA antibodies with a diagnosis of gluten sensitive enteropathy, does not reasonably provide enablement for any and all GSE-type or associated with gluten sensitive enteropathy or any and all antibodies for differential diagnosis or FXIIIA, TGk, TGx and Band 4.2 as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

7. Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3)

the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instantly recited claims are directed to a method for differential diagnosis of autoimmune diseases of the GSE-type or associated with gluten sensitive enteropathy comprising taking a sample and testing the sample for antibodies against human tissue transglutaminase and at least one other transglutaminase molecule selected from FXIIIA, TGk, TGx, TGe and Band 4.2.

The specification on page 6, lines 1-5 disclose ELISA's for detecting IgA anti-TG antibodies. Locke et al (J . Clinical Pathology, 1999; 52:274-277) teaches that tissue transglutaminase is a major autoantigen in celiac disease, and teaches that IgA (but not IgG) anti-tissue transglutaminase is closely associated with celiac disease in high titres but that low titres may not be disease specific. Thus, the specification does not show any and all antibodies to diagnose as recited. The specification on pages 12-15 of the specification disclose determining serum IgA levels in TGe and TGc ELISA's and comparing the results and showing that serum IgA antibodies from patients with CD and DH react with both the human TGc and the TGe, although the titres to TGe is lower. Both TGc and TGe can inhibit the reaction of serum IgA antibodies with TGc. Thus, showing that at least a part of the serum antibodies from patients with CD and DH is directed against epitopes which are shared by the two transglutaminases. Figure 6 and the specification on page 14, lines 10-22 discloses the serum concentrations of IgA

antibodies against TGc in the human TGc ELISA given in arbitrary units and teaches establishing a cutoff at 18 AU. Figure 6 discloses GSE diseases (CD and DH) and various other controls and diseases and the specification on page 14 discloses that the median antibody concentrations for the patients with untreated GSE (CD or DH) was 61.4 AU for controls 12 AU and that this difference was significant. However, as stated on page 14, a cutoff value of 18 AU was chosen, and sera with antibody concentrations equal or higher than 18 AU were labeled as human TGC ELISA positive. Thus, all of the diseases and controls in Figure 6 are positive to various degrees and further how could one skilled in the art differentiate coeliac disease (CD) from dermatitis herpetiformis (DH) as both appear to have the same amount of antibodies? The disclosure does not provide guidance on how to differentiate between diseases.

The specification on page 20, lines 16-17 of the specification discloses that "we conclude that the human TGC-based ELISA should be the method of choice for easy and non-invasive screening and diagnosis of GSE" and on page 22 discloses that "we provided a new method for diagnosis of autoimmune diseases of the GSE-type or associated with gluten sensitive enteropathy. The specification does not provide a definition for GSE-type nor does the specification specifically teach how diseases are associated with gluten sensitive enteropathy. The specification on page 21 discloses in Table 2 a list of autoimmune diseases that have been reported to associate with GSE and states that a part of the associations are proven, the other part have been anecdotal. The specification does not provide guidance on what is a GSE-Type autoimmune disease nor does the specification provide relevant association of these

diseases for differential diagnosis or provide evidence or data which could provide one of skill in the art of how to differentiate one disease listed in table 2 from the other disease. The specification also fails to provide any evidence concerning the presence and significance of auto-antibodies specific for or detectable by transglutaminases known as TGk, TGx, Factor XIIIA or band 4.2. There are no working examples provided in the specification. At best, a diagnosis of GSE can be determining only by testing a sample for IgA antibodies directed against human tissue transglutaminase and TGe and correlating increased amounts of the IgA antibodies with a diagnosis of gluten sensitive enteropathy. Thus, one skilled in the art cannot practice the invention without undue experimentation, because in order to have a high level of predictability, one skilled in the art would have to known what antibodies to test for and would also have to know what is considered to be a GSE-type disease or known how an autoimmune disease is associated with gluten sensitive enteropathy and would also have to have guidance on how to differentiate between the diseases.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is vague and indefinite because the preamble of the claim does not correlate with the body of the claim. The preamble of the claim recites a method for differential diagnosis of autoimmune disease of the GSE-type or associated with gluten

sensitive enteropathy. However, the body of the claim does not positively recite a step of differentially diagnosing autoimmune disease of the GSE-type or associated with gluten sensitive enteropathy. The body of the claim merely requires testing a sample for antibodies against human tissue transglutaminase and at least one other transglutaminase molecule selected from FXIIIA, TGk, TGx, TGe and Band 4.2.

Claim 13 the recitation "GSE-type" is vague and indefinite. The recitation "GSE-type" is not defined by the claim, nor does the specification provide a definition for the recitation. It is unclear what is meant by GSE-type.

Claim 13 is vague and indefinite because it is unclear how autoimmune diseases are associated with gluten sensitive enteropathy. The specification does not provide a definition for the term "associated". It is unclear what applicant intends by "associated with gluten sensitive enteropathy".

Claim 13 is vague and indefinite because it is unclear how testing the sample for antibodies as recited is correlated to a differential diagnosis. Does the mere presence of the antibodies indicate a differential diagnosis? Does and increase in antibodies against human tissue transglutaminase and a decrease of antibodies to the other molecules indicate a differential diagnosis. Does an increase in antibodies to both the human tissue transglutaminase and the other molecule indicate a differential diagnosis? Further, what is being differentially diagnosed? Is a GSE-type disease being differentiated from a disease associated with gluten sensitive enteropathy? Is a GSE-type disease being differentiated from GSE? If so how?

Claim 13 is vague and indefinite because of the use of acronyms: ie GSE, TGK TGe, etc.... Although the terms may have art-recognized meanings, it is unclear if applicant intends to claim the prior art definitions. The terms should be defined in their first instance.

Claim 13 the recitation "taking a sample" is indefinite. It is unclear what the sample is being taken from. Is the sample being taken from a container, a patient suspected of having a disease or an animal or a tissue? Please clarify.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claim 13 is rejected under 35 U.S.C. 102(b) or (e) as being anticipated by Schuppan et al (WO 98/03873 or US 6,319,726).

The WO and US references have the same disclosure. Schuppan et al disclose methods of detecting antibodies from body fluids by means of an immune reaction with tissue tranglutaminase (see '726 abstract). Schuppan et al disclose that the tissue transglutaminase can be human tissue transglutaminase (see '726, col 6, lines 20-22). Schuppan et al disclose that the tissue tranglutaminase can be immobilized and used to

detected antibodies in a sample for diagnosing celiac disease (GSE-Type, associated with GSE) (see '726, col 3). Schuppan et al disclose that the method is used to detect IgA antibodies.

With respect to the recitation "and at least one other transglutaminase molecule selected from FXIIIA, TGk, TGx, TGe and Band 4.2". Schuppan et al disclose that the antibodies to be detected are IgA antibodies which are against human tissue transglutaminase. These antibodies to be detected are the same as the antibodies detected by applicant (see specification). Thus, the antibodies of Schuppan et al would be cross reactive with other antigens and would inherently be against TGe. As shown by Applicant the IgA antibodies are cross reactive . The specification on page 15 discloses "the results shown support that serum IgA antibodes from patients with CD and DH react with both human TGc and TGe and further discloses that the serum antibodies from patients with CD and DH is directed against epitopes which are shared by the two transglutaminases". Thus, it is inherent that the IgA antibodies of Schuppan et al are against both human tissue transglutaminase and TGe. Further, as stated above the body of the claim merely requires a step of taking a sample and testing the sample for antibodies against human tissue transglutaminase and at least one other transglutaminase molecule. Also, as stated above it is unclear what is meant by GSE-type and associated diseases. Thus, for the above stated reasons Schuppan et al reads on the instantly recited claim.

Conclusion

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bazzigaluppi et al. (Journal of Autoimmunity (Feb. 1999) 12, 51-56) disclose measuring antibodies against human tissue transglutaminase (p.52, col 1).

Amin et al., (Clinica Chimica Acta 282 (April 1999) 219-225) disclose using guinea pig tTG as antigen to detect tTG antibodies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gary Counts
Examiner
Art Unit 1641
October 25, 2006

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